SUPPORTING INFORMATION

Efficient Determination of Free Energy Landscapes in Multiple Dimensions from Biased Umbrella Sampling Simulations Using Linear Regression

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COMPUTATIONAL DETAILS

Met-enkephalin is a small penta-peptide with the sequence YGGFM (Figure S1) and is used as a test case here. In the present study, Met-enkephalin was solvated in a cubic water box (1202 TIP3P[1] water molecules). The dimension of the entire system was 32 x 32 x 32 $Å^3$ and contained 3687 atoms. All MD simulations concerning Met-enkephalin were performed using version 2.8 of the MD package NAMD[2]. Umbrella sampling calculations were carried out using the Collective Variable module. CHARMM PARAM 27[3] force field was utilized in our simulation of Met-enkephalin. The isobaric-isothermal ensemble was employed for all MD calculations. The pressure and temperature were controlled by Langevin piston method and Langevin dynamics and kept at 1 bar and 300 K, respectively. Periodic boundary conditions were applied to the system. A cutoff of 12 Å was used to truncate the short-range non-bonded interactions, where a switching function was applied beyond 10 Å. Long-range interaction was treated by particle-mesh Ewald algorithm[4]. Covalent bonds involving a hydrogen atom were constrained to their equilibrium distances and a 2 fs time step was used in all calculations. Order parameters were defined as the two dihedral angles, $\phi 1$ and $\phi 2$, connecting the CA of residues 1 to 4 and residues 2 to 5, respectively. A graphical representation of both order parameters can be found in Figure S1. The force constant of the harmonic potentials applied to each order parameter is 0.02 kcal/mol·deg^2.

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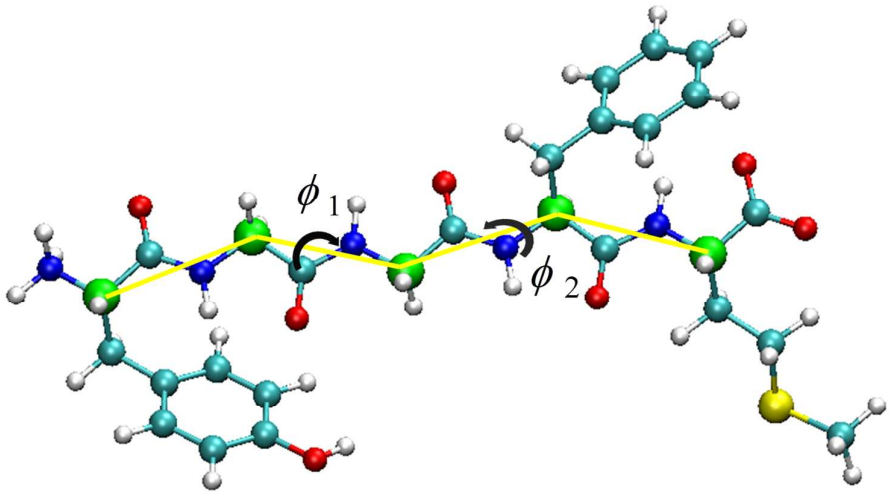

Figure S1: Structure of Met-enkephalin in stick-and-ball representation (from left to right, the amino acids are YGGFM in this figure). The Cα atoms of that peptide are marked in green color. The two order parameters used in umbrella sampling are $\phi_1 \equiv$ CA@Tyr1-CA@Gly2-CA@Gly3-CA@Phe4, and $\phi_2 \equiv$ CA@Gly2-CA@Gly3-CA@Phe4-CA@Met5.

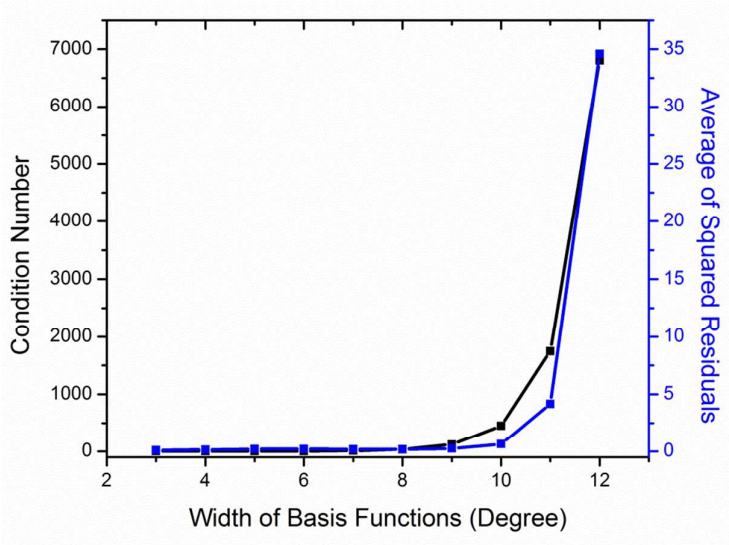

Figure S2: Condition number and average of squared residuals with respect of the width of basis functions (σ).

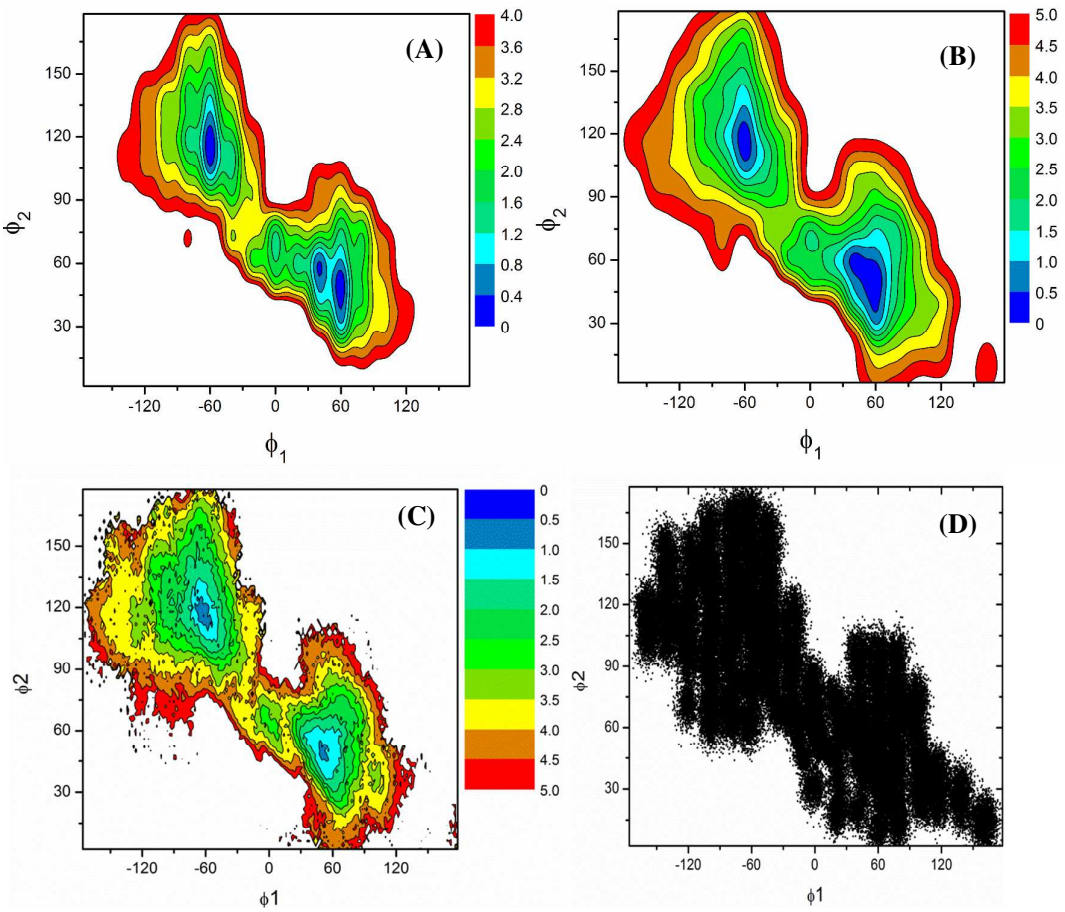

Figure S3: Free energy landscapes obtained from the linear model using 128 umbrella windows. (A) σ = 8°. (B) σ = 10°. (C) Free energy landscape yielded from WHAM using 128 umbrella windows. (D) A scatter plot of the time series from 128 windows. The unit of all free energy landscapes is in kcal/mol.

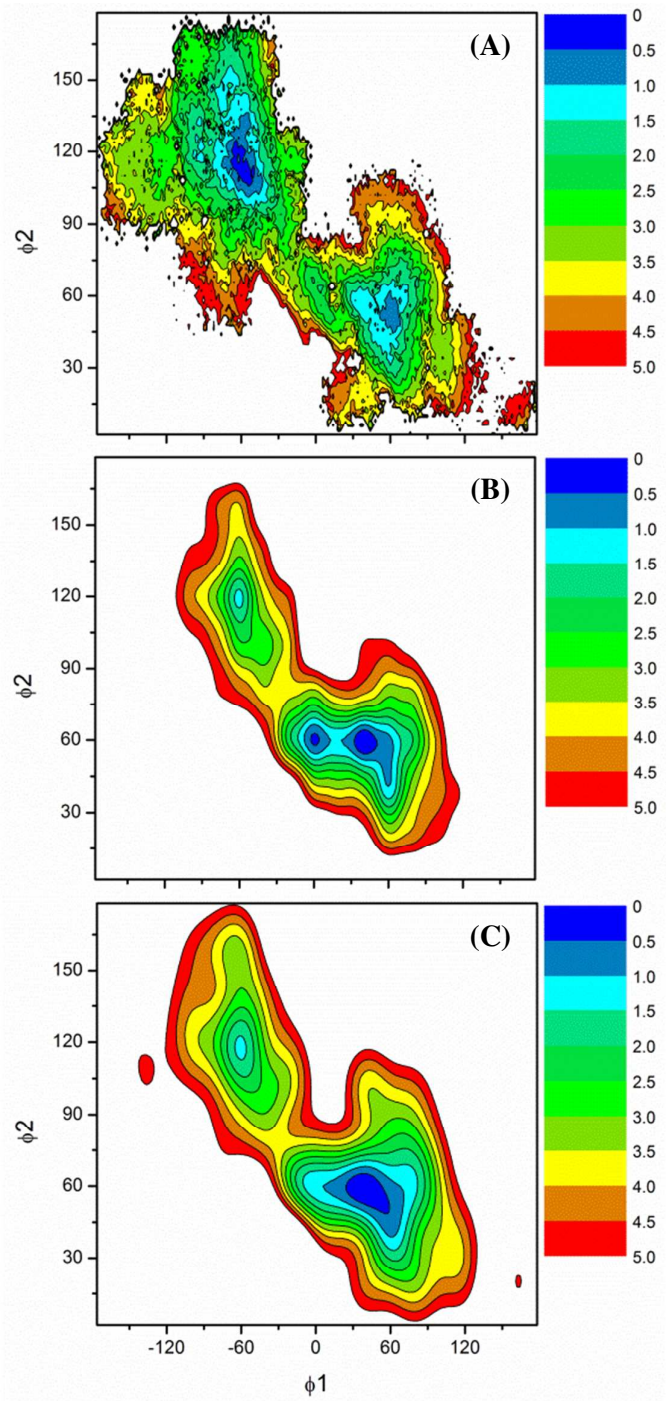

Figure S4: Free energy landscapes obtained from 67 umbrella windows. (A) PMF from WHAM. (B) Fitted PMF with σ = 10° (0.5 times of the new d_{us}). (C) Fitted PMF with σ = 15° (0.75 times of the new d_{us}). The unit of all free energy landscapes is in kcal/mol.

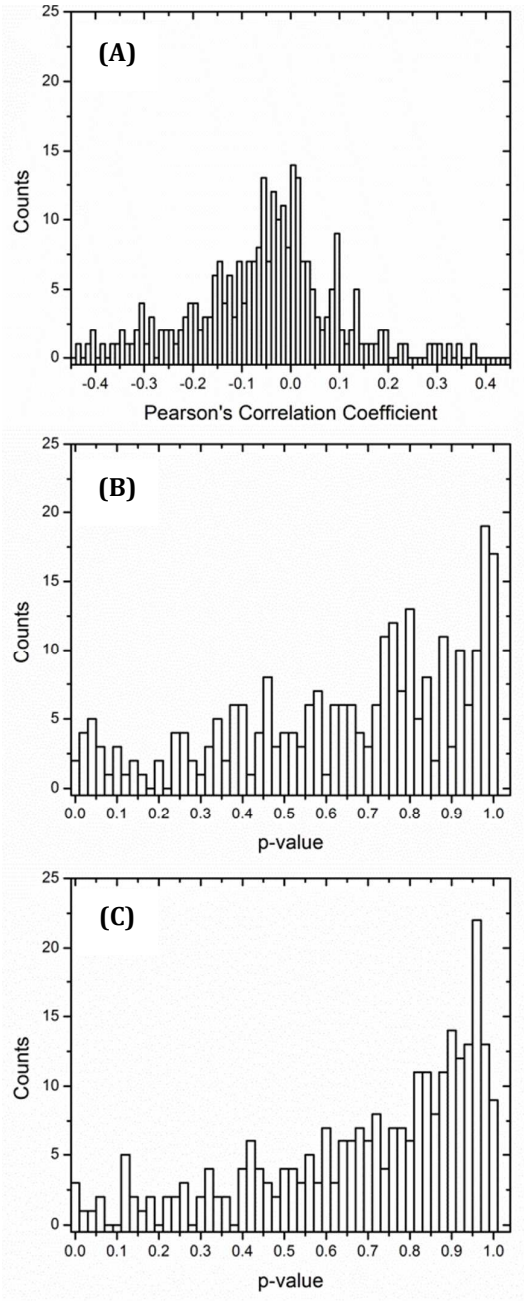

Figure S5: Histograms of Pearson's correlation coefficients and *p*-values from Kolmogorov-Smirnov tests. (A): Pearson's correlation coefficients. (B) *p*-values of $\phi 1$. (C) *p*-values of $\phi 2$.

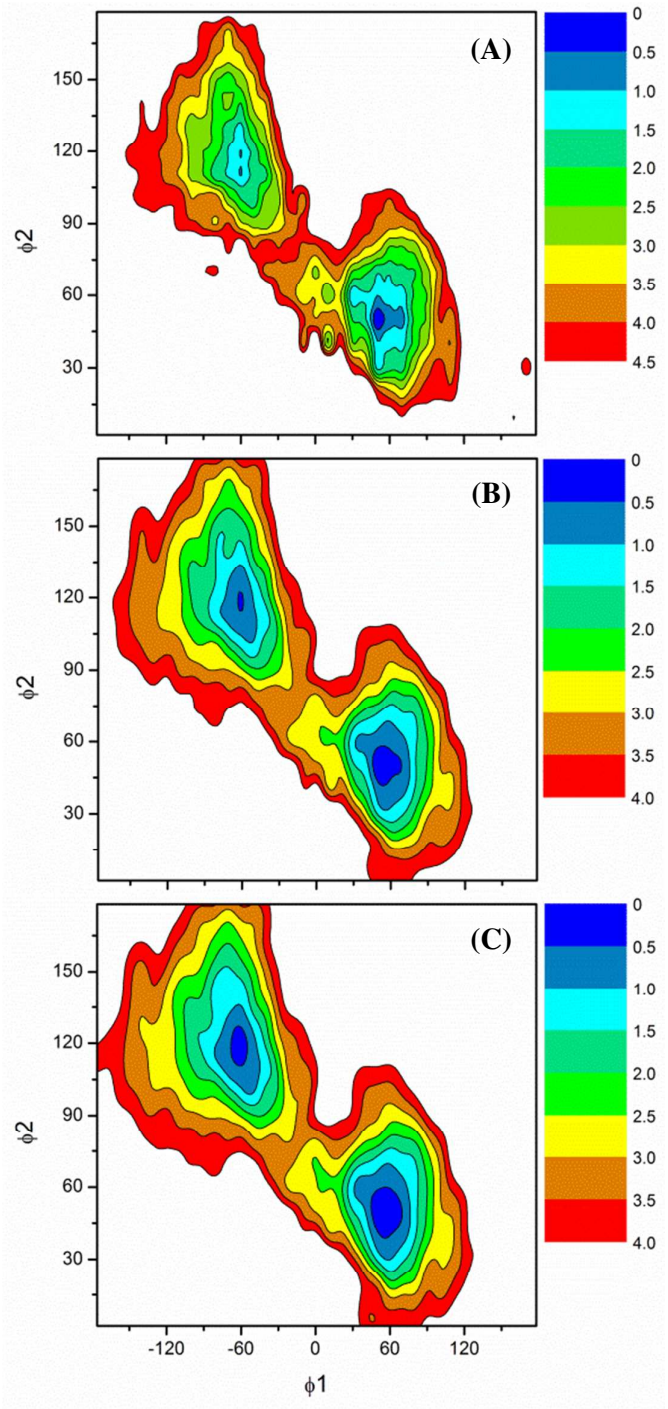

Figure S6: PMFs obtained from fitting mean forces <**F**>. (B) σ = 5°. (B) σ = 8°. (C) σ = 10°. All free energy landscapes are in the unit of kcal/mol.